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ELECTROCARDIOGRAPHIC AND BIOCHEMICAL ABNORMALITIES IN TAY-SACHS DISEASE*

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GANGLIOSIDES are a heterogeneous group of sphingoglycolipids which contain sialic acid. Tay-Sachs disease, or infantile amaurotic family idiocy, is a fatal inborn error of ganglioside metabolism.

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TABLE I. SUMMARY OF CARDIOVASCULAR EXAMINATION OF 12 PATIENTS WITH TAY-SACHS DISEASE

Patient No.	*Age (months)*	*Sex*	*Peripheral pulses*	*Peripheral cyanosis*	*Clubbing*
1.	12	M	N	+	0
2.	13	F	N	+	0
3.	21	M	N	+	0
4.	25	M	D	+	0
5.	26	M	N	+	+
6.	29	M	D	+	0
7.	31	F	N	+	0
8.	34	F	N	+	+
9.	31	M	N	+	0
10.	31	M	D	+	+
11.	37	F	D	+	+
12.	45	F	D	+	+

Abbreviations:
N = normal
D = decreased

The disorder, found mainly in descendants of Eastern European Jews, is characterized clinically by progressive psychomotor deterioration with severe pathological and biochemical changes in nervous tissue. Since in nerve tissue derived from patients who have Tay-Sachs disease there is a marked increase in the concentration of a normally minor ganglioside fraction G_5 or GM_2, the disorder is considered to be a GM_2 gangliosidosis.[1] Recent biochemical[2] and electron microscopic[3] studies of the liver in Tay-Sachs disease indicate that the metabolic defect may not be limited to nervous tissue.

Electrocardiographic and morphological changes have been reported in cases of the Hunter-Hurler syndrome[4] and in systemic late infantile amaurotic idiocy (GM_1 gangliosidosis).[5] These two diseases are associated with abnormal ganglioside patterns. The purpose of the present study was to determine whether the cardiovascular system was also affected in Tay-Sachs disease. Abnormal electrocardiographic patterns were found in eight of the 24 patients studied. Biochemical analysis of cardiac tissue obtained from autopsy from patients afflicted with Tay-Sachs disease revealed a ganglioside pattern similar to that found in the brain in the same disease.

TABLE I (continued) SUMMARY OF CARDIOVASCULAR EXAMINATION OF 12 PATIENTS WITH TAY-SACHS DISEASE

Patient	*Auscultatory findings*			*Murmurs*	*Chest x-ray cardiomegaly*
	First sound	*Second intensity*	*Sound split*		
1.	N	N	+	0	0
2.	N	N	0	0	0
3.	N	N	+	0	0
4.	N	N	0	0	0
5.	N	N	0	0	0
6.	N	N	0	0	0
7.	N	N	0	0	0
8.	N	N	0	0	0
9.	N	N	0	0	0
10.	N	N	+	0	0
11.	N	N	0	0	0
12.	N	N	0	0	0

Abbreviation:
N = normal

MATERIAL AND METHODS

The electrocardiographic records were analyzed in 24 cases of Tay-Sachs disease. Twelve of the 24 patients were alive at the time of the study (patients 1 through 12, Table I). The ages ranged from 10 to 45 months. Since the stereotyped clinical course and the pathological changes in the central nervous system have been correlated with age,[6] the patients were divided into three age groups.

Group I contained five patients (patients 1, 14, 20, 21, and 24), whose ages were less than 13 months. During this age span,Tay-Sachs disease is characterized clinically by the appearance of psychomotor arrest or deterioration or both.

Group II comprised five children (patients 2, 3, 16, 22, and 23) whose ages ranged from 13 to 24 months. During this period there are marked psychomotor deterioration, seizures, and megalocephaly.

The remaining 14 patients, all over two years of age (patients 4-13, 15, 17, 18, and 19) were placed in Group III. Children in this group were in a vegetative stage.

Patients were assigned to one of these three groups according to their

TABLE II. ELECTROCARDIOGRAPHIC FINDINGS OF 24 PATIENTS WITH TAY-SACHS DISEASE

Patient No.	*Age (months)*	*Heart rate*	*Rhythm*	*P = wave amplitude (mm.)*	*P-R interval (sec.)*
1.	12	140	RSR	1	0.10
2.	13	140	RSR	1.5	0.10
3.	21	120	SA	1	0.12
4.	25	150	RSR	1	0.12
5.	26	140	SA	1	0.12
6.	29	100	RSR	1	0.12
7.	31	100	RSR	1	0.12
8.	34	120	MSA	1	0.12
9.	31	100	RSR	1	0.12
10.	31	100	MSA	1	0.14
11.	37	80	MSA	1	0.14
12.	45	100	RSR	1	0.16
13.	44	140	RSR	1	0.12
14.	4	150	RSR	1	0.12
15.	27	140	RSR	2	0.12
16.	19	150	RSR	1	0.12
17.	44	150	RSR	3	0.16
18.	25	120	RSR	1	0.12
19.	35	150	RSR	1	0.12
20.	12	150	RSR	1	0.12
21.	9	130	RSR	1	0.10
22.	24	100	SA	1	0.12
23.	24	140	RSR	1	0.12
24.	9	150	RSR	1	0.12

age at the time of the study. Twelve of the 24 patients (patients 1 through 12, Table I) were observed continually during a period of two years by the same pediatric cardiologist. A routine 12-lead scalar electrocardiogram was recorded in each patient. Serial electrocardiograms were taken on eight patients. In 1 of the 8 (patient 11), tracings were available at 1, 2, and 3 years of age. In the remaining seven (patients 3, 4, 6, 8, 9, 10, and 12), 2 or 3 electrocardiograms were taken one month to 32 months after the initial electrocardiogram. Therefore the total number of electrocardiograms analyzed exceeds the number of patients in the study. While the electrocardiogram was being recorded in the

TABLE II (Continued) ELECTROCARDIOGRAPHIC FINDINGS OF 24 PATIENTS WITH TAY-SACHS DISEASE

Patient No.	*∠QRS frontal plane (degrees)*	*Ventricular hypertrophy*	*Q-Tc (sec.)*	*S-T segment Isoelectric*	*T wave*	*∠QRS-T angle (degrees)*
1.	+60	0	0.44*	+	N	56
2.	+60	0	0.44*	+	N	64*
3.	+60	0	0.45*	+	N	41
4.	+60	0	0.45*	elevated LP	P	30
5.	+90	0	0.43*	+	P	45
6.	+10	0	0.39	+	P	31
7.	+75	0	0.36	+	N	56
8	+60	0	0.40	+	N	48
9.	−30	0	0.41	+	P	74*
10.	+90	0	0.41	+	P	56
11.	+60	0	0.37	+	P	18
12.	+80	0	0.46*	+	P	24
13.	+75	0	0.42	+	P	74*
14	+60	0	0.44*	+	negative V_5	120*
15.	+70	0	0.42	+	N	28
16.	+75	0	0.38	+	N	44
17.	+120	0	0.43*	+	P	99*
18.	+80	0	0.41	+	negative V_5	95*
19.	+60	0	0.38	+	N	40
20.	+30	0	0.44*	+	N	15
21.	+75	0	0.45*	+	P	26
22.	+90	0	0.46*	+	N	65*
23.	+30	0	0.42	+	N	24
24.	+10	0	0.45*	+	N	31

Abbreviations:
RSR = regular sinus rhythm
SA = sinus arrhythmia
N = normal
* = above normal limits
MSA = marked sinus arrhythmia
LP = left precordium
P = peaked

precordial leads V_2 and V_6, phases of respiration were marked simultaneously in order to identify changes in QRS waves with respiration. The electrocardiograms on all 24 patients were analyzed for rate and rhythm, electrical axis, ventricular hypertrophy, amplitude and configuration of S-T segments and T waves, Q-Tc interval, and spatial QRS-T angle.[7]

Ganglioside concentration and patterns were determined in two

TABLE III. SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN 24 PATIENTS WITH TAY-SACHS DISEASE

Group No.	*Number of patients*	*Heart rate average/min.*	*Sinus arryhthmia*	*P = wave abnormalities*	*Prolonged P-R interval*
I.	5	144	none	none	none
II.	5	130	2	none	none
III.	14	120	3	1	none

fresh-frozen Tay-Sachs-disease hearts and in the heart of a young adult who died in sudden respiratory arrest. The cardiac lipids were extracted according to Folch et al.[8] The crude lipid extracts were applied to cellulose columns, and the gangliosides were eluted according to Rouser et al.[9] Aliquots of the ganglioside eluates were analyzed for total concentration of gangliosides by the method of Svennerholm.[10] Additional aliquots were spotted on thin layer plates prepared with Adsorbosil-3. The chromatography was carried out in chloroform-methanol-2.5 *N* ammonium hydroxide (65:35:5) followed by propanol-water (7:3). Both runs were ascending for seven hours each. The plates were developed with resorcinol.[10]

RESULTS

Table I summarizes the data obtained from the cardiovascular examination of the 12 living children. Peripheral cyanosis was observed in all 12 patients. Decreased peripheral pulses were found in five patients (patients 4, 6, 10, 11, and 12). Early clubbing was present in five patients (patients 5, 8, 10, 11, and 12). No abnormalities were found on auscultation. Chest x rays showed a normal heart size in all patients.

The electrocardiographic findings in the 24 patients studied are presented in Table II and are summarized according to age groups in Table III. Sinus arrhythmia was present in two patients (patients 3 and 22) of Group II, and was more pronounced in three others (patients 8, 10, and 11) of Group III. The P wave was normal in amplitude and duration in all patients except one (patient 17) of Group III. In this patient biatrial enlargement was diagnosed. The P-R interval was normal in all children, and none of the patients showed electrocardiographic evidence of ventricular hypertrophy. The Q-Tc interval was prolonged

TABLE III. (continued) SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS IN 24 PATIENTS WITH TAY-SACHS DISEASE

Group No.	*Abnormal ΔQRS (frontal plane)*	*Ventricular hypertrophy*	*Q-Tc >0.42 seconds*	*Abnormal S-T segment*	*T = wave abnormalities*	*SQRS-T angle >60°*
I.	none	none	5	none	2	1
II.	none	none	3	none	none	2
III.	2	none	4	1	10	4

in all patients of Group I (patients 1, 14, 20, 21, and 24); in three (patients 2, 3, and 22) of the five in Group II; and in four (patients 4, 5, 12, and 17) of the 14 in Group III. With the exception of one patient (patient 4) in Group III, no S-T segment displacement was found. The T wave was symmetrical and peaked in one patient (patient 21) in Group I, and 9 in Group III (patients 4, 5, 6, 9, 10, 11, 12, 13, and 17). Inverted T wave was found in one patient (patient 14) in Group I, and in one patient (patient 18) in Group III. An abnormal QRS-T angle[11] (wider than 60°) was found in one patient (patient 14) in Group I; in two patients (patients 2 and 22) in Group II; and in four patients (patients 9, 13, 17, and 18) in Group III. Prominent U waves were found in three patients (patients 2, 16, and 22). The S wave voltage recorded in precordial lead V_2 decreased significantly during inspiration in all patients, but was distinctly greater in those of Group III (Figure 1).

Serial electrocardiograms were taken on eight patients to 32 months after the initial record. A significant finding was the changes observed in the serial electrocardiograms in five of these eight patients (patients 4, 9, 10, 11, and 12). Figures 2 and 3, a montage of the electrocardiograms taken on two patients (patients 9 and 11), reveal that the changes in the configuration of the T wave indicative of abnormal repolarization are related to the age of the patient, i.e., to the stage of the disease. With progression of the disease, the abnormalities of repolarization become more pronounced. However, in one patient (patient 14), T-wave changes were seen as early as four months. In addition, marked sinus arrhythmias, not present initially, became prominent several months after the beginning of the disease in two patients (patients 10 and 11).

Biochemical analysis revealed that the average concentration of sialic

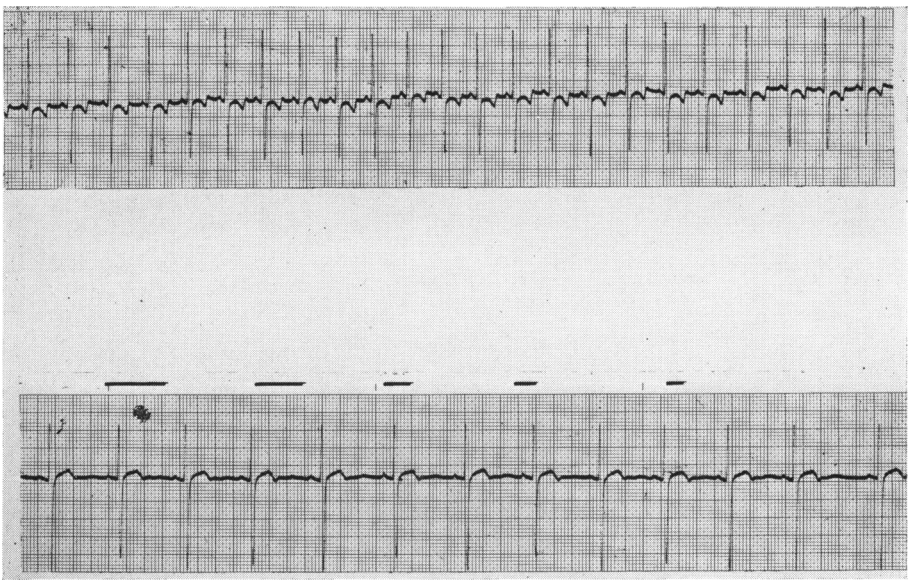

Fig. 1. The upper tracing corresponds to patient 1 at 12 months of age. The lower tracing corresponds to patient 12 at 45 months of age. Both tracings were recorded in precordial lead V_2. The interrupted marks at the top of the tracing indicate inspiration. All patients showed significant decrease in the voltage of the S wave during inspiration; this was more pronounced in older children.

acid in the heart in cases of Tay-Sachs disease was 418 μg. per gram wet weight. The control concentration of sialic acid in cardiac tissue was 63 μg. per gram wet weight. Thin layer chromatography of heart tissues in Tay-Sachs disease revealed a marked increase in the ganglioside fraction, the Rf value of which was similar to the G5 (GM_2) fraction in the brain in Tay-Sachs disease. This pattern was not seen in the control heart (Figure 4).

Discussion

This study indicates that the cardiovascular system is frequently affected in Tay-Sachs disease. Of the 24 patients studied eight were considered to have atypical or abnormal electrocardiographic findings. Many of the children, especially those in Group III, had more than one electrocardiographic abnormality. No single electrocardiographic pattern was found to be pathognomonic of Tay-Sachs disease. Because of the unequal distribution of patients in the three age groups, it was

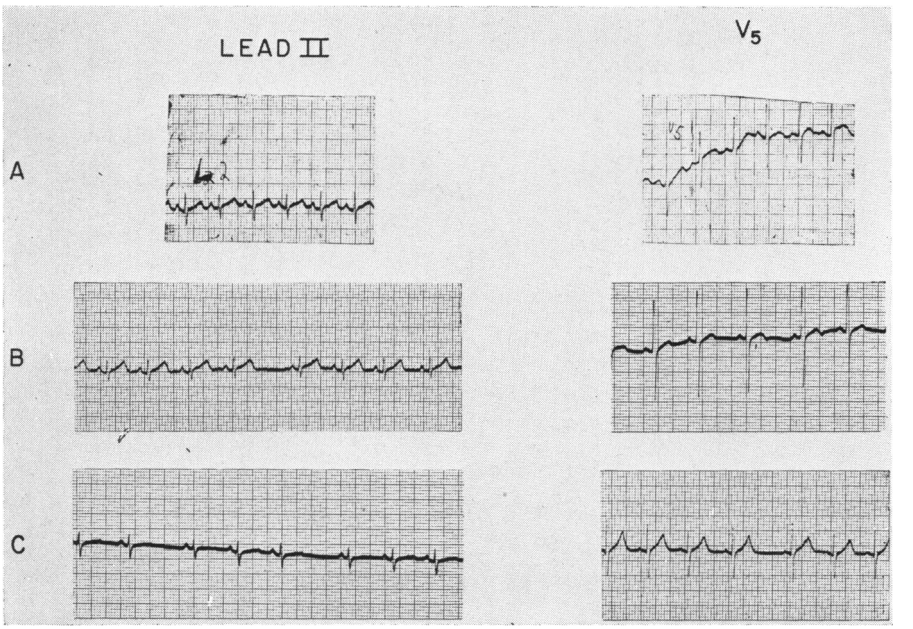

Fig. 2. Lead II and precordial lead V_5 recorded in patient 9 at 18 months (*A*); 25 months (*B*); and 30 months (*C*). Note the change in T-wave configuration during the different stages of the disease.

impossible to prove statistically that there was a positive correlation between the number and type of electrocardiographic abnormalities and the stage of the disease. However, the serial electrocardiograms taken on eight patients during a period of two years suggest that there was a positive correlation between the nature of the electrocardiographic abnormalities and the age of the patient (Figure 2).

The wide QRS-T angle, the prolonged Q-Tc interval, and the development of peaked T waves which are manifestations of abnormal repolarization, were found in patients in all three groups (Table III). It has recently been demonstrated that a wide QRS-T angle is frequently associated with cardiomyopathy.[12, 13] A wide QRS-T angle was noted in eight of the 24 cases studied. Six of these eight were in Group III.

These electrocardiographic abnormalities, indicative of an abnormal process of repolarization, and perhaps cardiomyopathy, may be due to primary cardiac involvement or may be secondary to the various

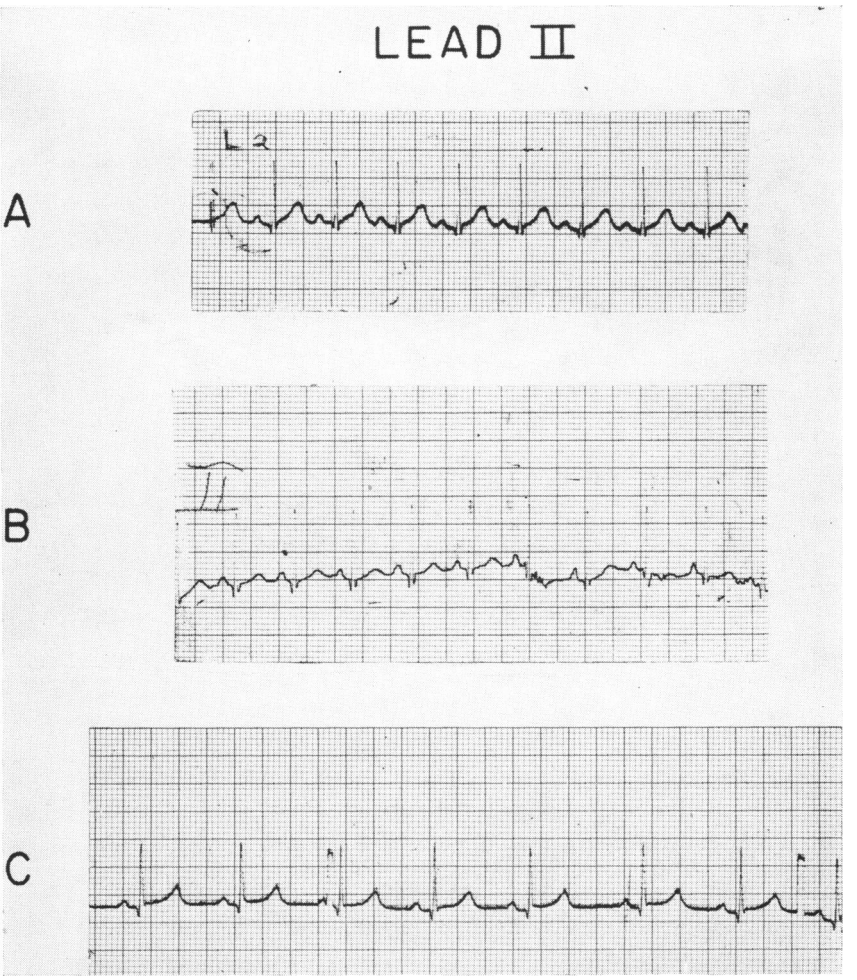

Fig. 3. Lead II of patient 11 recorded at one year (*A*); two years (*B*); and three years (*C*). Note the development of symmetrical peaked T waves.

complications associated with the disease. Respiratory distress and pneumonia are frequent in Tay-Sachs disease. Arterial O_2 saturation studies in 24 patients with Tay-Sachs disease revealed that 23 had a pO_2 of less than 90 mm. Hg.[14] The cyanosis and clubbing seen in our series are consistent with hypoxia. Further, the marked changes in amplitude of the S wave in precordial lead V_2 during the different phases of respiration are also evidence of respiratory disturbance in these patients

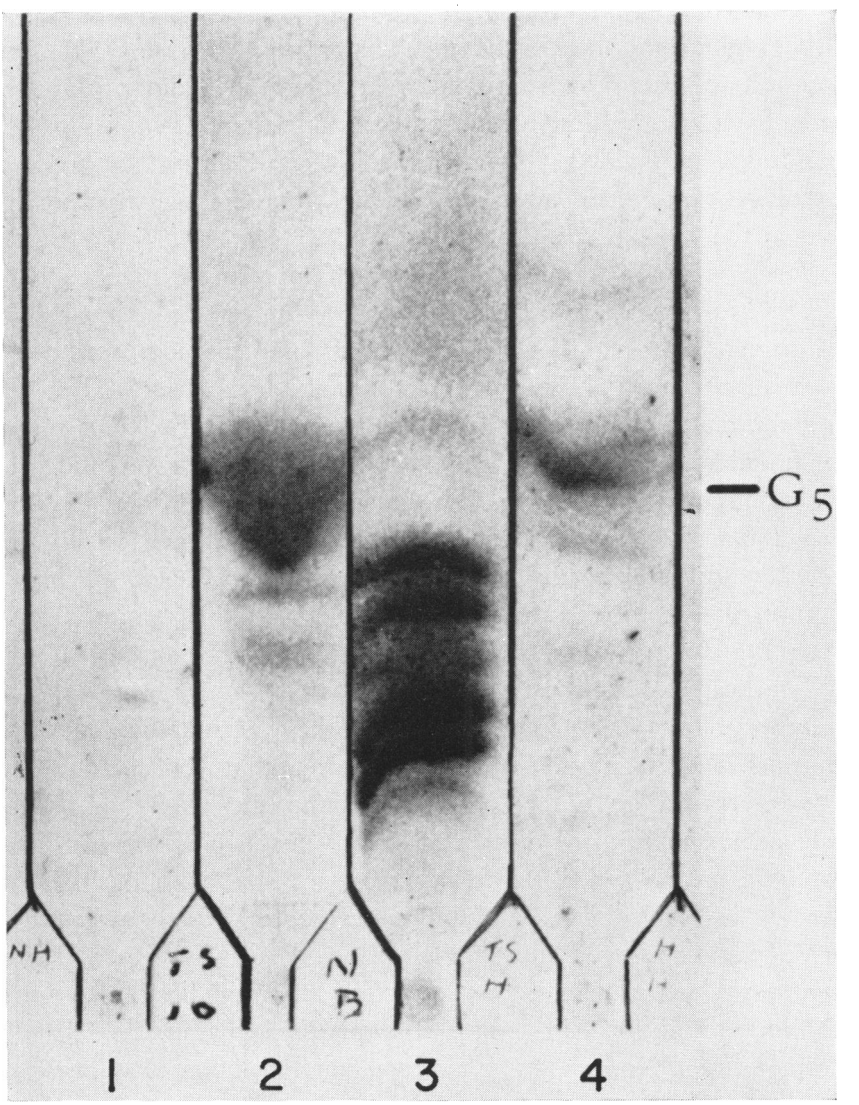

Fig. 4. 1 = normal heart; 2 = brain from a case of Tay-Sachs disease; 3 = normal brain; 4 = heart from a case of Tay-Sachs disease. The major ganglioside fraction in Tay-Sachs heart is G5. This pattern is not seen in normal hearts.

(Figure 1). The changes were more pronounced with advancing age. Respiratory difficulties also increase with the age of the patient. As demonstrated by Lamb,[15] the changes in voltage of S_2 correspond to changes in the stroke volume of the left ventricle. Thus the electrocardiographic abnormalities may be secondary to hypoxia. On the other hand it has been shown that electrocardiographic abnormalities can result from various lesions in the central nervous system.[16, 17, 18] It should also be noted that the sinus arrhythmia seen in Tay-Sachs disease may be produced by increased vagal tone, and suggests involvement of the vagus nerve.

There is also biochemical evidence of myocardial involvement in Tay-Sachs disease. Cardiac tissue derived from patients who had had Tay-Sachs disease had a sixfold increase of sialic acid compared to control cardiac tissue. Thin layer chromatography of the heart in Tay-Sachs disease revealed an abnormally high concentration of a lipid fraction which had an Rf value similar to that of G_5 (GM_2) ganglioside. This is the fraction that is markedly increased in the brain in Tay-Sachs disease. Gangliosides are important constituents of cell membranes[19] and they can alter the excitability of nerve cells.[20] Conceivably the electrocardiographic manifestations of abnormal repolarization could be due to the abnormal concentration of cardiac ganglioside.

The hearts of four patients included in the study were examined at autopsy. In two of these four cases the electrocardiograms were abnormal. The gross and light microscopic findings on all four hearts were interpreted as normal. This appears to be strong prima facie evidence against primary myocardial involvement in Tay-Sachs disease. However, until recently a similar situation existed with regard to the liver in Tay-Sachs disease. With light microscopy the liver in Tay-Sachs disease was considered morphologically and histochemically normal. However, electron microscopy revealed abnormal lipid cytosomes,[12] and biochemical analysis showed abnormal and characteristic ganglioside patterns.[2] Svennerholm[10] therefore concluded that Tay-Sachs disease was a systemic disorder of ganglioside metabolism.

In conclusion, electrocardiographic abnormalities were found in 29% of Tay-Sachs disease patients. In addition there was biochemical evidence of G_5 (GM_2) ganglioside accumulation in the heart in Tay-Sachs disease. Electrocardiographic and biochemical abnormalities in the heart, along with the electron microscope and biochemical abnor-

malities in the liver, indicate that Tay-Sachs disease is a systemic disorder.

Summary

The present study analyses the electrocardiographic findings in 11 male and 13 female children who had Tay-Sachs disease. None of the patients had evidence of associated congenital or acquired heart disease. Twelve of the 24 children were alive at the time of the study. Since the clinical and pathological findings in Tay-Sachs disease show a close correlation with age, the electrocardiograms were analyzed according to age groups. Group I (0-12 months) and Group II (13-24 months) consisted of five patients each, and Group III (above 25 months) consisted of 14 patients. Serial electrocardiograms were taken in eight of the 24 patients one to 32 months after the initial tracing.

One patient in Group I, two in Group II, and five in Group III had evidence of abnormal repolarization. Serial electrocardiograms revealed that the T-wave changes indicative of abnormal repolarization had a positive correlation with the age of the patient. Three patients in Group III displayed marked sinus arrhythmia.

Ganglioside concentration and patterns were determined at autopsy on two freshly frozen hearts in cases of Tay-Sachs disease and in the heart of a young adult who died in sudden respiratory arrest. In the Tay-Sachs heart, the average concentration of sialic acid was 418 μg. gram wet weight as compared to 63 μg. gram wet weight in the control. Thin layer chromatography revealed a marked increase in that ganglioside fraction, with an Rf similar to the G5 (GM_2) fraction of the Tay-Sachs brain. The ganglioside abnormality in the Tay-Sachs heart was, therefore, similar to that in the Tay-Sachs brain. In contrast, the predominent ganglioside fractions in the normal heart were G4 (GM_1) and G6 (GM_3).

These observations indicate that the cardiovascular system is affected in patients with Tay-Sachs disease. It is proposed that cardiovascular studies be performed in all patients with lipid storage disease.

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